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=> d his ful

     FILE 'HCAPLUS' ENTERED AT 16:16:01 ON 28 DEC 2005
                  E WHITTLE ROBERT R/AU
L42            93 SEA ABB=ON  ("WHITTLE ROBERT"/AU OR "WHITTLE ROBERT L"/AU OR
                  "WHITTLE ROBERT R"/AU OR "WHITTLE ROBERT RICHARD"/AU)
                  E SANCILIO FREDERICK D/AU
L43            31 SEA ABB=ON  ("SANCILIO F D"/AU OR "SANCILIO FRED D"/AU OR
                  "SANCILIO FREDERICK D"/AU)
                  E STOWELL GRAYSON WALKER/AU
L44            31 SEA ABB=ON  ("STOWELL GRAYSON W"/AU OR "STOWELL GRAYSON
                  WALKER"/AU)
                  E JENKINS DOUGLAS JOHN/AU
L45            18 SEA ABB=ON  ("JENKINS DOUGLAS"/AU OR "JENKINS DOUGLAS J"/AU OR
                  "JENKINS DOUGLAS JOHN"/AU)
                  E WHITTALL LINDA B/AU
L46            19 SEA ABB=ON  ("WHITTALL LINDA"/AU OR "WHITTALL LINDA B"/AU)
L47             8 SEA ABB=ON  L42 AND L43 AND L44 AND L45 AND L46
L48             7 SEA ABB=ON  L47 AND ?PHARM?
L49             7 SEA ABB=ON  L48 AND ?BENZIMIDAZOL?
                  SELECT RN L49 1-7

     FILE 'REGISTRY' ENTERED AT 16:18:49 ON 28 DEC 2005
L50            47 SEA ABB=ON  (73590-58-6/BI OR 119141-88-7/BI OR 161796-77-6/BI
                  OR 161796-78-7/BI OR 95510-70-6/BI OR 119141-89-8/BI OR
                  7585-39-9/BI OR 12619-70-4/BI OR 161973-10-0/BI OR 57-55-6/BI
                  OR 371758-94-0/BI OR 372518-59-7/BI OR 7439-95-4/BI OR
                  109-99-9/BI OR 110268-21-8/BI OR 122985-54-0/BI OR 1336-21-6/BI
                   OR 14807-96-6/BI OR 151-21-3/BI OR 25212-88-8/BI OR 272118-55-
                  5/BI OR 4070-80-8/BI OR 497-19-8/BI OR 55589-62-3/BI OR
                  557-04-0/BI OR 64-17-5/BI OR 67-56-1/BI OR 67-64-1/BI OR
                  67-66-3/BI OR 68-12-2/BI OR 69-65-8/BI OR 75-05-8/BI OR
                  75-09-2/BI OR 7558-79-4/BI OR 7631-86-9/BI OR 7646-69-7/BI OR
                  7693-27-8/BI OR 77-93-0/BI OR 7786-30-3/BI OR 78-93-3/BI OR
                  9003-39-8/BI OR 9004-34-6/BI OR 9004-38-0/BI OR 9004-57-3/BI
                  OR 9004-64-2/BI OR 9004-67-5/BI OR 9005-65-6/BI)

     FILE 'HCAPLUS' ENTERED AT 16:18:56 ON 28 DEC 2005
L51             7 SEA ABB=ON  L49 AND L50

     FILE 'REGISTRY' ENTERED AT 16:30:07 ON 28 DEC 2005
L52                STRUCTURE 73590-58-6
L53             5 SEA SSS SAM L52
L54            95 SEA SSS FUL L52  95 compds for str. 2 (see "d que stat", attached)
L55             1 SEA ABB=ON  73590-58-6/RN  RN for str. 1
The 2 compds are tautomers, so it is retrieved as one comp'd.
     FILE 'HCAPLUS' ENTERED AT 16:34:24 ON 28 DEC 2005
L56          3317 SEA ABB=ON  L54 OR L55
*L57         1759 SEA ABB=ON  L56 AND (PRD<19990826 OR PD<19990826)  1759 cits from CA Plus
                  SAV L57 GRA021L57/A
* this search statement is saved, should you want to see additional hits)

***(other searches were performed from 158-185)

     FILE 'HCAPLUS' ENTERED AT 17:28:37 ON 28 DEC 2005
L86            467 SEA ABB=ON  L57 AND ?PHARM?
L87            178 SEA ABB=ON  L86 AND (?ORAL? OR PO)  (printed 159-178))
                  178 cits from CA Plus
     FILE HOME
                                                per telephone conversation
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FILE HCAPLUS

FILE COVERS 1907 - 28 Dec 2005 VOL 144 ISS 1
FILE LAST UPDATED: 27 Dec 2005 (20051227/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 27 DEC 2005 (20051227/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 will soon be available. For details on the 2005 reload, enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 21 December 2005 (20051221/ED)

FILE CANCERLIT
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 22 Dec 2005 (20051222/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE JAPIO
FILE LAST UPDATED: 7 DEC 2005 <20051207/UP>
FILE COVERS APR 1973 TO AUGUST 25, 2005

<<< GRAPHIC IMAGES AVAILABLE >>>

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 28 DEC 2005 (20051228/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Dec 2005 (20051227/PD)
FILE LAST UPDATED: 27 Dec 2005 (20051227/ED)
HIGHEST GRANTED PATENT NUMBER: US6981281
HIGHEST APPLICATION PUBLICATION NUMBER: US2005283878
CA INDEXING IS CURRENT THROUGH 27 Dec 2005 (20051227/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Dec 2005 (20051227/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 DEC 2005 HIGHEST RN 870676-46-3
DICTIONARY FILE UPDATES: 27 DEC 2005 HIGHEST RN 870676-46-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=> d que stat l87
L52             STR
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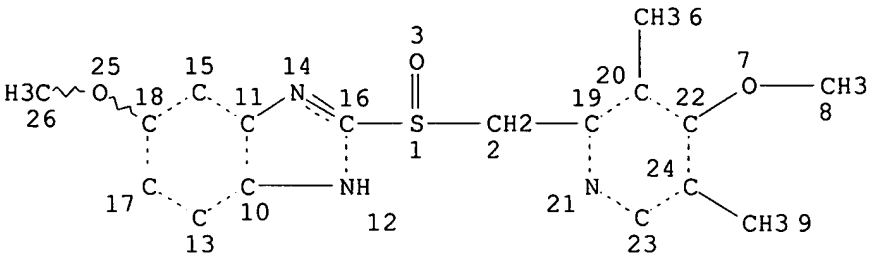


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  24

STEREO ATTRIBUTES: NONE
L54           95 SEA FILE=REGISTRY SSS FUL L52
L55            1 SEA FILE=REGISTRY ABB=ON  73590-58-6/RN
L56         3317 SEA FILE=HCAPLUS ABB=ON  L54 OR L55
L57         1759 SEA FILE=HCAPLUS ABB=ON  L56 AND (PRD<19990826 OR PD<19990826)

L86          467 SEA FILE=HCAPLUS ABB=ON  L57 AND ?PHARM?
L87          178 SEA FILE=HCAPLUS ABB=ON  L86 AND (?ORAL? OR PO)
```

=> d ibib abs l87 159-178

L87 ANSWER 159 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:614884 HCAPLUS
DOCUMENT NUMBER: 115:214884
TITLE: Antiulcer rectal preparations containing omeprazole
INVENTOR(S): Kim, Kwang Sik
PATENT ASSIGNEE(S): Hanmi Pharm. Ind. Co., Ltd., S. Korea
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 444625	A1	19910904	EP 1991-102856	19910226 <--
EP 444625	B1	19940608		
R: CH, DE, ES, FR, GB, IT, LI, SE				
CA 2037101	AA	19910828	CA 1991-2037101	19910226 <--
CA 2037101	C	19970318		
ES 2057628	T3	19941016	ES 1991-102856	19910226 <--
JP 04234817	A2	19920824	JP 1991-119605	19910227 <--
JP 07051503	B4	19950605		
US 5219870	A	19930615	US 1991-661652	19910227 <--
PRIORITY APPLN. INFO.:			KR 1990-2526 A	19900227 <--

AB The title preparation comprises (1) omeprazole (I), (2) a mixture of polyethylene glycol-1000, -1540, -4000, or -6000 as a water-soluble base or a mixture of fatty acid, fatty acid ester, and Na lauryl sulfate as a lipid-soluble base, and (3) a stabilizer selected from arginine, lysine, and histidine. When I is **orally** administered, it is easily decompomposed under the pH of stomach and an enteric-coated preparation requires more time in arriving at the effective serum concentration; therefore, this stabilized composition allows its efficacy by absorption through a neutral or weak alkaline pH media in the rectum. A composition contained I 20, arginine 10, and a mixture of polyethylene glycol 970 mg and its color was unchanged for > 7 days at 50° in 75% relative humidity.

L87 ANSWER 160 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:589755 HCAPLUS
DOCUMENT NUMBER: 115:189755
TITLE: **Pharmaceutical** composition and methods for treating the symptoms of overindulgence
INVENTOR(S): Goldman, William J.; Gates, Thomas N.
PATENT ASSIGNEE(S): McNeil-PPC, Inc., USA
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 426479	A1	19910508	EP 1990-311995	19901101 <--
EP 426479	B1	19940216		

R: AT, BE, CH, DE, ES, FR, GB, IT, LI

IN 171746	A	19921226	IN 1990-CA907		19901029 <--
CA 2028746	AA	19910503	CA 1990-2028746		19901031 <--
CA 2028746	C	19951226			
AU 9065689	A1	19910509	AU 1990-65689		19901031 <--
AU 646230	B2	19940217			
ZA 9008775	A	19920729	ZA 1990-8775		19901101 <--
AT 101515	E	19940315	AT 1990-311995		19901101 <--
ES 2057439	T3	19941016	ES 1990-311995		19901101 <--
JP 03206052	A2	19910909	JP 1990-298713		19901102 <--
US 5204118	A	19930420	US 1992-876824		19920429 <--
IN 176327	A	19960427	IN 1992-CA757		19921016 <--
US 5417980	A	19950523	US 1994-268865		19940629 <--
PRIORITY APPLN. INFO.:			US 1989-430837	A	19891102 <--
			IN 1990-CA907	A1	19901029 <--
			EP 1990-311995	A	19901101 <--
			US 1992-876824	A3	19920429 <--
			US 1993-46534	B1	19930413 <--

AB **Pharmaceutical** compns. which can relieve the symptoms of overindulgence, such as headache and acid indigestion, comprise (1) acetaminophen or a nonsteroidal antiinflammatory drug and (2) histamine H1 or H2 receptor blocker, proton pump inhibitor, or a combination thereof. The composition can be in the form of tablets, capsules, or liqs. Thus, a tablet contained acetaminophen 500, cimetidine 150 mg, and other auxiliary agents and coloring agents.

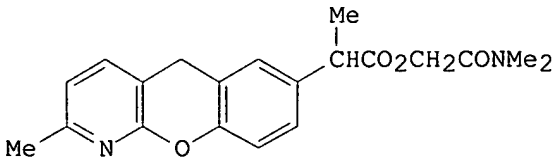
L87 ANSWER 161 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:624073 HCAPLUS
DOCUMENT NUMBER: 113:224073
TITLE: **Pharmacokinetics** of various single intravenous and **oral** doses of omeprazole
AUTHOR(S): Andersson, T.; Cederberg, C.; Regaardh, C. G.; Skaanberg, I.
CORPORATE SOURCE: Res. Lab., AB Haessle, Moelndal, S-43183, Swed.
SOURCE: European Journal of Clinical Pharmacology (**1990**), 39(2), 195-7
CODEN: EJCPAS; ISSN: 0031-6970
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of dose on the kinetics of omeprazole and two of its metabolites, hydroxyomeprazole and the sulfone, has been studied. Ten healthy subjects were given omeprazole 10 and 40 mg i.v. and 10, 40 and 90 mg **orally**. No significant dose-related difference in any parameter calculated from the i.v. expts. was detected. Following the **oral** solns., however, there was a dose-dependent increase in systemic availability, probably due to saturable first-pass elimination. The AUC of the sulfone also seemed to increase non-linearly with increasing dose, and that of the hydroxyomeprazole increased in proportion to dose. The slight dose-dependency of the bioavailability of the solution is considered to be of no or limited clin. relevance. Furthermore, since omeprazole is given **orally** as slowly absorbed enteric coated granules in the dose of 20 mg once daily, the potential for dose-dependent kinetics in clin. practice would be much less than in the present study.

L87 ANSWER 162 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:446208 HCAPLUS
DOCUMENT NUMBER: 113:46208
TITLE: **Pharmacokinetics** and bioavailability of omeprazole after single and repeated **oral** administration in healthy subjects

AUTHOR(S): Andersson, Tommy; Andren, K.; Cederberg, C.; Lagerstroem, P. O.; Lundborg, P.; Skaanberg, I.
CORPORATE SOURCE: Res. Lab., AB Haessle, Moelndal, S-431 83, Swed.
SOURCE: British Journal of Clinical Pharmacology (**1990**), 29(5), 557-63
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ten healthy subjects were given 20 mg omeprazole EC (enteric-coated) granules once daily for 3 days. An i.v. tracer dose of [14C]-omeprazole was given simultaneously with the first and last **oral** doses and blood sampling was performed thereafter. In order to study the extent of absorption at minimal acid exposure, a single dose of 20 mg omeprazole was also given as a buffered solution, before and after the treatment with EC granules. Kinetic parameters of omeprazole after the i.v. tracer dose were unchanged on repeated dosing while AUC increased by approx. 40% for the solution and 60% for the EC granules. The increased AUC is caused by an increased systemic availability, which may be explained by a decreased first-pass elimination during repeated treatment and/or by a reduced degradation of omeprazole in the stomach secondary to the profound decrease in intragastric acidity caused by the drug. Thus, the antisecretory effect of therapeutic doses of omeprazole must be studied during repeated administration and not judged from studies using single doses only.

L87 ANSWER 163 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:185639 HCAPLUS
DOCUMENT NUMBER: 112:185639
TITLE: Effect of gastric acidity on bioavailability of N,N-dimethylcarbamoylmethyl α,2-dimethyl-5H-[1]benzopyrano[2,3-b]pyridine-7-acetate, a new prodrug-type anti-inflammatory agent
AUTHOR(S): Yamada, Ichimaro; Goda, Tomoko; Kawata, Miwako; Mizuta, Hiroaki; Ogawa, Kenji; Yokobe, Testuo
CORPORATE SOURCE: Res. Lab., Yoshitomi Pharm. Ind., Ltd., Fukuoka, 871, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (**1989**), 37(12), 3372-5
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The effect of gastric acidity on the bioavailability of the title compound (I), as pranoprofen prodrug, a new anti-inflammatory agent, was investigated in gastric acidity-controlled beagle dogs. The dissoln. rates of this compound in media of pH 1.2 and 3.0 were greater than those in media of pH 5.0 and 6.8. Reflecting these dissoln. characteristics, the peak plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC0-12h) were reduced by shifting the gastric acidity to low levels (>pH

6) with omeprazole treatment. In designing dosage forms of I, it is necessary to develop **pharmaceutical** prepns. whose bioavailability is not affected by the gastric acidity.

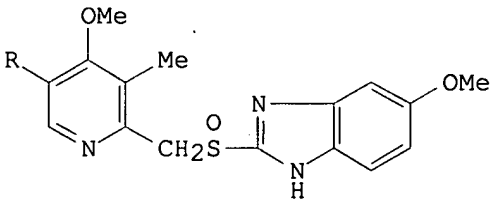
L87 ANSWER 164 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:151234 HCAPLUS
DOCUMENT NUMBER: 112:151234
TITLE: The **pharmacokinetics** of omeprazole in humans - a study of single intravenous and **oral** doses
AUTHOR(S): Regaardh, C. G.; Andersson, T.; Lagerstroem, P. O.; Lundborg, P.; Skaanberg, I.
CORPORATE SOURCE: Haessle Res. Lab., Moelndal, S-431 83, Swed.
SOURCE: Therapeutic Drug Monitoring (**1990**), 12(2), 163-72
CODEN: TDMODV; ISSN: 0163-4356
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **pharmacokinetics** of omeprazole, hydroxyomeprazole, omeprazolesulfone, and "remaining metabolites" were studied in 8 young healthy subjects following an acute i.v. and **oral** dose of 10 and 20 mg of 14C-labeled drug, resp. The **oral** dose was given as a buffered solution Two subjects exhibited essentially higher and more sustained plasma levels of omeprazole than the others. This was due to a higher bioavailability, lower clearance, and longer t1/2 of omeprazole in these two subjects. Maximum concentration (0.7-4.6 μmol/L) was reached between 10 and 25 min after **oral** dosing. The median bioavailability was 39% (25-117%) and the median systemic plasma clearance was 624 mL/min (range of 59-828 mL/min). The corresponding t1/2 for the i.v. dose was 35 min (16-150 min) and 39 min (14-186 min) after **oral** administration. The drug was rapidly distributed to extravascular sites. Mean Vss was 0.23 L/kg. Low systemic clearance of omeprazole was associated with a decreased formation rate of hydroxyomepraxole and "remaining metabolites" while omeprazole-sulfone formation seemed to be less affected. However, there was a clear-cut correlation between the t1/2 of omeprazole and of its omeprazolesulfone metabolite, indicating that the elimination of these two compds. is mediated by the same isoenzyme. The mean urinary recovery of the radioactive dose during 96 h was 78.3 and 75.7% for the i.v. and **oral** dose, resp. Insignificant amts. were due to unchanged drug and omeprazolesulfone. The excretion of hydroxyomeprazole during the first 12 h varied between 4.6 to 15.5% of a given dose. The mean recovery of radioactivity in the feces was 19.3% of a given i.v. dose and 18.2% when given **orally**. Omeprazole is mainly eliminated metabolically and there is a substantial interindividual variation in the rate of formation of primary and secondary metabolites. This variation in omeprazole disposition is probably of limited clin. importance. The half-life, with a maximum of .apprx.3 h, is too short to cause accumulation when the drug is administered in a once-daily regimen.

L87 ANSWER 165 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:111535 HCAPLUS
DOCUMENT NUMBER: 112:111535
TITLE: Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole
AUTHOR(S): Andersson, Tommy; Cederberg, Christer; Edvardsson, Gunilla; Heggelund, Asger; Lundborg, Per
CORPORATE SOURCE: Res. Lab., AB Haessle, Moelndal, S-431 83, Swed.
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO,

United States) (**1990**), 47(1), 79-85
CODEN: CLPTAT; ISSN: 0009-9236
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of omeprazole treatment on diazepam plasma levels was studied in four slow and six rapid metabolizers of omeprazole. Single i.v. doses of diazepam (0.1 mg/kg) were administered after 1 wk of **oral** treatment with omeprazole (20 mg) and placebo. This was a double-blind crossover study with randomized placebo and omeprazole treatments. Blood was collected up to 120 h after diazepam dosing (still during one-daily omeprazole and placebo administration) for measurement of diazepam and its major metabolite desmethyldiazepam. The slow metabolizers of omeprazole also metabolized diazepam slowly, exhibiting only half the diazepam plasma clearance of the others. The mean clearance of diazepam was decreased 26% after omeprazole in the rapid metabolizers, whereas the slow group showed no apparent interaction. The mean plasma concns. of desmethyldiazepam showed a more rapid formation in the rapid compared with the slow metabolizers, which is a logical consequence of the rate of diazepam metabolism

L87 ANSWER 166 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:165454 HCAPLUS
DOCUMENT NUMBER: 110:165454
TITLE: Identification of two main urinary metabolites of [14C]omeprazole in humans
AUTHOR(S): Renberg, Lars; Simonsson, Roger; Hoffmann, Kurt Juergen
CORPORATE SOURCE: Dep. Pharmacokinet. Drug Metab., AB Hoessle, Molndal, Swed.
SOURCE: Drug Metabolism and Disposition (**1989**), 17(1), 69-76
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I, R=Me
II, R=CH_2OH
III, R=CO_2H

AB The excretion and metabolism of [14C]-labeled omeprazole (I) given **orally** as a suspension was studied in 10 healthy male subjects. An average of 79% of the dose was recovered in the urine in 96 h, with most of the radioactivity (76% of dose) being eliminated in the first 24 h. Pooled urine (0-2 h) from 5 subjects, containing about 47% of the dose, was analyzed by reversed-phase gradient elution liquid chromatog. with radioisotope detection. I was completely metabolized to at least 6 metabolites. The 2 major metabolites were extensively purified by liquid chromatog. and their structures were determined by mass spectroscopy with derivatization and use of stable isotopes, 1H NMR, and comparison with synthetic refs. They were formed by hydroxylation of a Me group in the pyridine ring, followed by further oxidation of the alc. to the corresponding carboxylic acid. Both metabolites retained the sulfoxide group of I,

rendering them as unstable as the parent compound at pH <7. They accounted for approx. 28% (hydroxyomeprazole) (II) and 23% (omeprazole acid) (III) of the amount excreted in the 0-2 h collection interval. Based on in vitro studies with the synthetic metabolites in isolated gastric glands, it is unlikely that II and III will contribute to the **pharmacol**. effect of I in humans.

L87 ANSWER 167 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:28994 HCAPLUS
DOCUMENT NUMBER: 110:28994
TITLE: Gastric acid antisecretory effect of two different dosage forms of omeprazole during prolonged **oral** treatment in the gastric fistula dog
AUTHOR(S): Larsson, Haakan; Mattsson, H; Carlsson, E.
CORPORATE SOURCE: Dep. Biol., AB Haessle, Moelndal, S-431 83, Swed.
SOURCE: Scandinavian Journal of Gastroenterology (**1988**), 23(8), 1013-19
CODEN: SJGRA4; ISSN: 0036-5521
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two series of experiment were performed in gastric fistula dogs to test the antisecretory effect of two different **oral** dosage forms of omeprazole (I): a Me cellulose suspension and enteric-coated granules (ECG). There was an increasing inhibitory effect during the first days of repeated administration of I, which is in accordance with its long duration of action. The steady-state inhibitory level was reached after 5 doses. During the 8-wk treatment with the I suspension (2 μmol + kg-1) the mean maximal inhibitory level (3 h after dose) was 82%, and the mean minimal inhibitory level (24 h after dose) was 35%. With I in ECG (0.5 μmol + kg-1) steady-state maximal inhibition (4th h) ws 60%, whereas 40% inhibition remained after 24 h. Thus, a more even inhibitory level over day and night seems to be obtained with the ECG formulation than with the suspension. Basal and food-stimulated plasma gastric levels were not significantly affected by the treatment with 0.5 μmol + kg-1, whereas food-stimulated gastric levels were slightly increased during treatment with 2 μmol + kg-1. Control levels of acid secretion were reached within 4 days of stopping treatment. In the present studies, in which the inhibition of acid secretion varied over 24 h between approx. 80 and 35% (maximum and min.), no rebound effects could be detected as measured as measured up to 1 mo after cessation of treatment.

L87 ANSWER 168 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:431889 HCAPLUS
DOCUMENT NUMBER: 109:31889
TITLE: Rat parietal cell function after prolonged inhibition of gastric acid secretion
AUTHOR(S): Larsson, Haakan; Carlsson, Enar; Ryberg, Birgitta; Fryklund, Jan; Wallmark, Bjoern
CORPORATE SOURCE: Dep. Biol., Haessle Gastrointest. Res. Lab., Moelndal, S-431 83, Swed.
SOURCE: American Journal of Physiology (**1988**), 254(1, Pt. 1), G33-G39
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Female rats were treated **orally** for 3 mo with omeprazole (40 and 400 μmol/kg). Both doses caused total inhibition of gastric acid secretion and recovery was parallel to that of H+-K+-ATPase activity (30-50 and 60-80% inhibition 24 h after doses, resp.). The H+-K+-ATPase activity returned to control levels within 1 wk after the last dose.

Plasma gastrin levels were dose-dependently increased during treatment but reversed to control levels within 9 days after the last dose. Parallel with a general increase in corpus mucosal mass, both pepsinogen and H+-K+-ATPase total content increased. However, their tissue concns. did not differ from control values, suggesting that neither parietal nor chief cell d. are changed by omeprazole treatment and also that their growth is parallel to the general hyperplasia. In contrast, the oxyntic mucosal histamine concentration was increased, indicating an increase in the enterochromaffin-like (ECL) cell d. Maximum capacity of the mucosa to secrete acid increased in parallel with the increase in mucosal mass and total H+-K+-ATPase content. However, basal acid secretion did not differ between treatment groups. Increased capacity slowly declined toward control levels over the 70-day recovery period after withdrawal of omeprazole. Thus, hypergastrinemia, induced in the rat by **pharmacol.** inhibition of gastric acid secretion, causes a hyperplasia of oxyntic mucosal cells, ECL cells growing faster than the others. The hyperplastic mucosa has an increased capacity to produce acid and is functionally normal.

L87 ANSWER 169 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:215779 HCAPLUS
DOCUMENT NUMBER: 108:215779
TITLE: The interaction of omeprazole with rat liver cytochrome P 450-mediated monooxygenase reactions in vitro and in vivo
AUTHOR(S): Chenery, R. J.; Ayrton, A.; Oldham, H. G.; Norman, S. J.; Standring, P.
CORPORATE SOURCE: Smith Kline and French Res. Ltd., Welwyn/Kent., UK
SOURCE: Biochemical Pharmacology (**1988**), 37(7), 1407-14
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of omeprazole on cytochrome P 450-mediated monooxygenase reactions was assessed in the rat liver S9 system, utilizing ethylmorphine-N-demethylase (EM) and ethoxycoumarin-O-deethylase (ECOD) activities. The inhibition of EM by omeprazole was predominantly reversible in mechanism. The average Ki for omeprazole was 40 μM with EM and 76 μM with ECOD. In prepns. of rat hepatocytes, the intrinsic clearance of diazepam was decreased substantially by 50 μM omeprazole (average inhibition 73%). In comparison, 50 μM cimetidine inhibited the intrinsic clearance of diazepam by 50%. The relationship between these 2 in vitro models for drug interactions is discussed in the context of previously published drug inhibition data. Moreover, repeated administration of omeprazole to adult male rats (500 mg/kg, 14 days, **orally**) resulted in increases in liver weight, cytochrome P 450, and ECOD activity. Thus, omeprazole interacts with the mixed-function oxidase system in vitro and in vivo.

L87 ANSWER 170 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:68339 HCAPLUS
DOCUMENT NUMBER: 108:68339
TITLE: Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules
AUTHOR(S): Tuynman, H. A. R. E.; Festen, H. P. M.; Roehss, K.; Meuwissen, S. G. M.
CORPORATE SOURCE: Dep. Gastroenterol., Free Univ. Hosp., Amsterdam, Neth.
SOURCE: British Journal of Clinical Pharmacology (**1987**), 24(6), 833-5

CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Healthy human subjects were studied after a single **oral** dose of 20 mg omeprazole given as enteric-coated granules with and without concomitant administration of 10 mL of a potent liquid antacid under fasting conditions. No significant differences were detected in various **pharmacokinetic** parameters of the drug when given with and without antacid.

L87 ANSWER 171 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:18820 HCAPLUS
DOCUMENT NUMBER: 108:18820
TITLE: A new in vivo method for repeatedly studying gastric acid secretion and other secretory parameters in awake guinea pig
AUTHOR(S): Batzri, Shmuel; Harmon, John W.; Dubois, Andre; Moskowitz, Debbie; Weichbrod, Robert; Rich, Norman M.
CORPORATE SOURCE: Dep. Surg., Univ. Health Sci., Bethesda, MD, 20814, USA
SOURCE: Journal of Surgical Research (**1987**), 43(5), 398-406
CODEN: JSGRA2; ISSN: 0022-4804
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A model for measuring gastric secretory parameters in awake guinea pigs is described. A chronic cannula was surgically implanted in the stomach of each guinea pig. The rates of gastric secretion and changes in intragastric volume were measured using a dye dilution technique. In contrast to previous techniques in small laboratory animals, there was no collection of gastric juice via drainage, no **oral** intubation for aspiration was involved, no special or sophisticated equipment was used, no anesthesia was employed, and there was no stress associated with acute surgery. This method offers a valuable advantage by combining the chronic gastric cannula with a dye dilution technique in that the same animal can be used several times and finally, several gastric secretory parameters can be measured simultaneously. The animals were used from 3 wk to 10 mo after surgery and as many as 15 studies were performed on the same guinea pig. Samples were collected at 10-min intervals and analyzed for acid and dye concentration from which the onset and kinetics of gastric secretion were followed. Basal gastric secretion (11.8 μeq/kg/min) was increased within 20 min after s.c. infusion of histamine (30 μg/kg/h) and peaked by 40-60 min at a mean acid output rate of 41 μeq/kg/min. Histamine also increased the intragastric volume from 6.3 to 13.4 mL as it increased fluid output from 1.6 mL/10 min to 3.4 mL/10 min. The increase in acid output caused by histamine was inhibited by the H2-antagonists cimetidine (3 μmole/kg) and ranitidine at 0.5 μmole/kg. Omeprazole (1.2 μmole/kg), an H-K-ATPase inhibitor, almost abolished acid output under both basal and histamine-stimulated conditions. Thus, the present method is simple and suitable to study the physiol. and **pharmacol**. of gastric secretion in the guinea pig with a particular emphasis on the action of histamine. Furthermore, because of the species involved, there is also a significant economical advantage and the guinea pig can also be used as a potential model for studying exptl. ulcer.

L87 ANSWER 172 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:417822 HCAPLUS
DOCUMENT NUMBER: 105:17822
TITLE: Comparative metabolic disposition of **oral** doses of omeprazole in the dog, rat, and mouse

AUTHOR(S): Hoffmann, Kurt Juergen; Renberg, Lars; Olovson, Stig Goeran
CORPORATE SOURCE: Dep. Pharmacokinet. Drug Metabol., AB Haessle, Moelndal, S-431 83, Swed.
SOURCE: Drug Metabolism and Disposition (**1986**), 14(3), 336-40
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The metabolic disposition of 14C-labeled omeprazole [**73590-58-6**] was studied in dogs, rats, and mice after the administration of **pharmacol**. active, single **oral** doses of drug in buffer solns. (pH 9). Avs. of 38% (dogs), 43% (rats), and 55% (mice) of the radiolabeled doses were excreted in the urine in 72 h. Most of the remaining dose was recovered in the feces. Omeprazole was extensively metabolized in all species studied and the metabolites were eliminated rapidly. No unchanged drug could be detected in the urine samples (<0.1% of dose). In each species at least 10 metabolites were detected in urine (pH 9) by gradient elution reverse phase HPLC. Based on liquid chromatog. retention data, the metabolic patterns were very complex and exhibited some quant. differences between species. Bile was collected from rats and from chronic bile-fistulated dogs. Biliary excretion was a major route of elimination of omeprazole metabolites, and four polar metabolites were detected in the rat bile. The stability of omeprazole metabolites at varying pH values is discussed with reference to reductive metabolism of the parent compound

L87 ANSWER 173 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:28399 HCAPLUS
DOCUMENT NUMBER: 104:28399
TITLE: Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro
AUTHOR(S): Gugler, Roland; Jensen, J. Chris
CORPORATE SOURCE: Dep. Med., Univ. Bonn, Bonn, 5300/1, Fed. Rep. Ger.
SOURCE: Gastroenterology (**1985**), 89(6), 1235-41
CODEN: GASTAB; ISSN: 0016-5085
DOCUMENT TYPE: Journal
LANGUAGE: English
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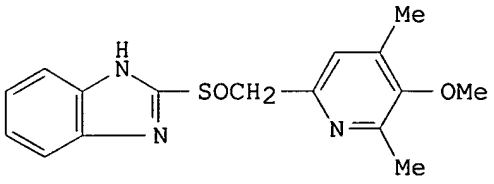


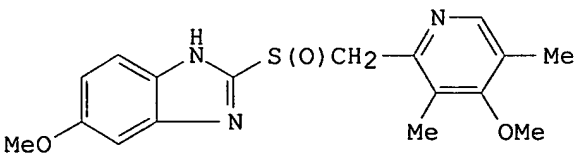
I

AB The effect of omeprazole (I) [**73590-58-6**] on the elimination of diazepam [439-14-5] and phenytoin [57-41-0] was studied in healthy subjects. Omeprazole given **orally** in a daily dose of 40 mg over 7 days decreased diazepam plasma clearance and prolonged the half-life of diazepam. Plasma concns. of desmethyldiazepam [1088-11-5], a diazepam metabolite, were reduced after omeprazole treatment. Omeprazole also reduced the plasma clearance of phenytoin and prolonged its half-life.

Renal excretion of the major metabolite of phenytoin (p-hydroxyphenyl-phenyl-hydantoin [2784-27-2]) was not changed. Omeprazole did not affect the volume of distribution and the plasma protein binding of either diazepam or phenytoin. In vitro studies with human liver microsomes showed that omeprazole in equimolar concns. (0.5 mM) was a stronger inhibitor than cimetidine of 7-ethoxycoumarin deethylase [42613-26-3] activity. These data confirm that omeprazole interferes with the elimination of other drugs by an inhibition of the drug metabolizing monooxygenase [9038-14-6] system of the human liver.

L87 ANSWER 174 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:553787 HCAPLUS
DOCUMENT NUMBER: 103:153787
TITLE: Antisecretory effect and **oral pharmacokinetics** following low dose omeprazole in man
AUTHOR(S): Howden, C. W.; Forrest, J. A. H.; Meredith, P. A.; Reid, J. L.
CORPORATE SOURCE: Univ. Dep. Mater. Med., Stobhill Gen. Hosp., Glasgow, G21 3UW, UK
SOURCE: British Journal of Clinical Pharmacology (**1985**), 20(2), 137-9
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of single and repeated doses of omeprazole [**73590-58-6**] (10 mg) on gastric secretion were studied in a group of 6 healthy subjects. Single doses had no effect on basal or stimulated acid output. After 7 days of treatment, there was a 93.1% reduction in basal acid output and a 66.5% reduction in stimulated output. Pepsin output was not affected. Systemic availability of omeprazole, as reflected in the area under curve, increased with repeated dosing. Thus, low doses of omeprazole can produce substantial redns. in acid output after repeated dosing.

L87 ANSWER 175 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:89907 HCAPLUS
DOCUMENT NUMBER: 102:89907
TITLE: Omeprazole: a study of its inhibition of gastric pH and **oral pharmacokinetics** after morning or evening dosage
AUTHOR(S): Prichard, Peter J.; Yeomans, Neville D.; Mihaly, George W.; Jones, D. Brian; Buckle, Peter J.; Smallwood, Richard A.; Louis, William J.
CORPORATE SOURCE: Dep. Gastroenterol., Univ. Melbourne, Heidelberg, Australia
SOURCE: Gastroenterology (**1985**), 88(1, Pt. 1), 64-9
CODEN: GASTAB; ISSN: 0016-5085
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB In 8 healthy subjects omeprazole (I) [**73590-58-6**] was administered **orally** as an encapsulated enteric-coated granulate (40 mg daily at 9 AM or 9 PM for 5 days), and its effect on the integrated 24-h gastric pH was determined, together with its apparent bioavailability. The pretreatment 24-h median pH was 1.9. After 5 days of treatment, the median pH had risen to 5.0. with morning dosage and 4.5 with evening dosage. This corresponded to a >99% reduction in 24-h median hydrogen ion activity, with morning dosage having a greater effect (from 9 AM to 8 PM) than evening dosage. The relative bioavailability of omeprazole increased 2-fold from day 1 to day 5 of treatment with morning dosage and 3-fold with evening dosage, suggesting that increased absorption of this acid-labile drug occurs with increasing inhibition of acid secretion. Thus, this formulation of omeprazole presently being used in clin. trials is a highly potent antisecretory agent.

L87 ANSWER 176 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1984:583381 HCAPLUS
DOCUMENT NUMBER: 101:183381
TITLE: **Oral pharmacokinetics** of omeprazole
AUTHOR(S): Howden, C. W.; Meredith, P. A.; Forrest, J. A. H.; Reid, J. L.
CORPORATE SOURCE: Univ. Dep. Materia Med., Stobhill Gen. Hosp., Glasgow, UK
SOURCE: European Journal of Clinical Pharmacology (**1984**), 26(5), 641-3
CODEN: EJCPAS; ISSN: 0031-6970
DOCUMENT TYPE: Journal
LANGUAGE: English
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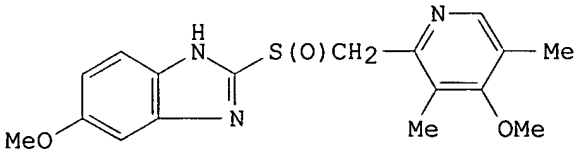

I

AB The **pharmacokinetics** of omeprazole (I) [**73590-58-6**] were studied in a group of healthy male subjects after single and repeated **oral** doses of 30 and 60 mg. Absorption of omeprazole from its enteric-coated formulation was unpredictable. There was a highly significant increase in the area under the plasma concentration time curve (AUC) after repeated dosing. Omeprazole increased its own relative bioavailability following repeated dosing. This may be due to inhibition of gastric acid secretion by the drug which is an acid-labile compound

L87 ANSWER 177 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:172935 HCAPLUS
DOCUMENT NUMBER: 98:172935
TITLE: Effect of omeprazole, a gastric proton pump inhibitor, on pentagastrin stimulated acid secretion in man
AUTHOR(S): Lind, Tore; Cederberg, Christer; Ekenved, Gunnar; Haglund, Ulf; Olbe, Lars

CORPORATE SOURCE: Dep. Surg. II, Univ. Goeteborg, Goeteborg, S-413 45, Swed.
SOURCE: Gut (**1983**), 24(4), 270-6
CODEN: GUTTAK; ISSN: 0017-5749
DOCUMENT TYPE: Journal
LANGUAGE: English
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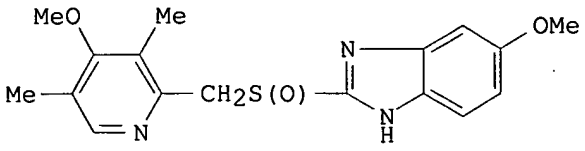

I

AB The effect of **oral** omeprazole (I) [**73590-58-6**] on pentagastrin stimulated gastric acid secretion was studied in healthy subjects. Doses of 20-80 mg produced dose-dependent inhibition of acid secretion, with total suppression at the highest dose. Omeprazole was absorbed and eliminated from plasma rapidly and the inhibitory effect was related to the area under the plasma concentration time curve. The duration of action was long and single doses of 20 and 40 mg reduced acid secretion significantly for 1 and 3 days, resp. Omeprazole in a dose of 15 mg given once daily for 5 days, suppressed acid secretion continuously, the inhibitory effect stabilizing after 3 days at a predose inhibition of about 30% and a postdose inhibition of about 80%.

L87 ANSWER 178 OF 178 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:205422 HCAPLUS
DOCUMENT NUMBER: 96:205422
TITLE: **Pharmaceutical** use of benzimidazoles
INVENTOR(S): Ruwart, Mary Jean
PATENT ASSIGNEE(S): Upjohn Co. , USA
SOURCE: Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 45200	A1	19820203	EP 1981-303416	19810724 <--
EP 45200	B1	19880302		
R: BE, CH, DE, FR, GB, IT, NL, SE				
US 4359465	A	19821116	US 1980-173233	19800728 <--
JP 57053406	A2	19820330	JP 1981-118378	19810728 <--
JP 01060008	B4	19891220		
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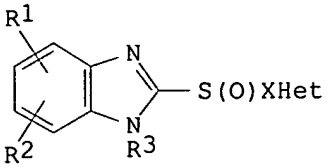

I

AB **Oral pharmaceutical** compns. for prevention or treatment of nongastric acid-induced, nontraumatically-induced, nonneoplastic gastrointestinal inflammatory disease in a mammal comprise the title compds. I [R1 and R2 = H, C1-4 alkyl, halogen, CN, CO2H, etc.; R3 = H, C1-4 alkyl, alkylcarbonyl, CONH2, etc.; X = alkylene, Het = heterocyclic, or XHet taken together = R4R5R6C6H2CHR7 (R4, R5, and R6 = H, Me, MeO, EtO, etc.; R7 = H, Me, or Et] and their salts. The ED50 for inhibition of gastric acid secretion in rats fasted with restraint for 36 h by timoprazole (I, R1, R2, R3 = H, X = CH2, Het = 2-pyridyl)(II) [57237-97-5] in a vehicle containing Emulphor 10, EtOH 10, and H2O 80% was 12 mg/mL. A batch of 10,000 tablets each containing 10 mg II were prepared